

AWARD NUMBER: **W81XWH-15-1-0378**

TITLE: **Improving Survival and Promoting Respiratory Motor Function after Cervical Spinal Cord Injury**

PRINCIPAL INVESTIGATOR: **Warren J. Alilain, Ph.D.**

CONTRACTING ORGANIZATION: **UNIVERSITY OF KENTUCKY**
LEXINGTON KY 40526-0001

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14. ABSTRACT Most spinal cord injuries (SCI) occur near the neck. The cervical level of the spinal cord is located near this area. At this level are the connections to the cells which instruct the diaphragm, the major muscle used for breathing, to contract. Therefore, damage at the cervical level can lead to a paralyzed diaphragm and an inability to breathe and inspire air. Patients who survive this type of injury often need the use of a mechanical ventilator in order to survive. Use of the ventilator severely limits the quality of life of those injured and dramatically increases the demand for health care. However, despite these drastic interventions, the cervical injured patient is still susceptible to death due to respiratory complications. This application proposes to help improve survival, decrease early dependence on mechanical ventilation, and restore breathing after cervical spinal cord injury, as well as develop prognostic indicators for injury progression and recovery. Through these studies we endeavor to add to the standard of care for cervical SCI patients so as to lead to an improved quality of life, better-quality health care management, and improved functional outcomes.					
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1. Introduction

Most spinal cord injuries (SCI) occur near the neck. The cervical level of the spinal cord is located near this area. At this level are the connections to the cells which instruct the diaphragm, the major muscle used for breathing, to contract. Therefore, damage at the cervical level can lead to a paralyzed diaphragm and an inability to breathe and inspire air. Patients who survive this type of injury often need the use of a mechanical ventilator in order to survive. Use of the ventilator severely limits the quality of life of those injured and dramatically increases the demand for health care. However, despite these drastic interventions, the cervical injured patient is still susceptible to death due to respiratory complications. This application proposes to help improve survival, decrease early dependence on mechanical ventilation, and restore breathing after cervical spinal cord injury, as well as develop prognostic indicators for injury progression and recovery. Through these studies we endeavor to add to the standard of care for cervical SCI patients so as to lead to an improved quality of life, better-quality health care management, and improved functional outcomes.

2. Keywords

SCI, breathing, phrenic, variability, axon, regeneration, neurotrauma

3. Accomplishments

What are the major goals of the project?

The major goals of the project are to:

- 1) Obtain regulatory review and approval by USAMRMC Animal Care and Use Review Office (ACURO) and local Institutional Animal Care and Use Committee (IACUC).
- 2) Test the hypothesis that inhibiting PTEN through bpV will promote recovery of respiratory motor function after cervical SC contusion.
- 3) Test the hypothesis that increasing respiratory drive immediately after cervical contusion will promote survival and independence immediately after cervical SCI.
- 4) Test the hypothesis that respiratory motor patterns and variability are surrogate endpoints that accurately predict functional improvement after cervical SC contusion and intervention.

What was accomplished under these goals?

As the Science Officer, Dr. Quntian Wang, and Grants Specialist, Amber Stillrich, are aware, I recently changed institutions and am now located in the Spinal Cord and Brain Injury Research Center at the University of Kentucky in Lexington, KY. This move was effective 10/1/15.

In this environment, I have colleagues with primary research interests in neurotrauma, including spinal cord injury. Additionally, there is a common goal of improving recovery after central nervous system injury. This setting can only help to improve this project by having an interactive and vibrant group with considerable insight and experience help discuss findings and encountered pitfalls.

However, with this move there has been a delay in obtaining approval of an award transfer. This was just recently attained 8/16/16.

We did accomplish the first major goal of the project which was obtaining regulatory review and approval by the USAMRMC Animal Care and Use Review Office (ACURO) and the local Institutional Animal Care and Use Committee (IACUC) at the University of Kentucky. IACUC approval was obtained 2/22/16. ACURO approval was later attained 3/24/16.

What opportunities for training and professional development did the project provide?
Nothing to Report.

How were the results disseminated to communities of interest?
Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals and objectives?
With the grant contract successfully transferred to UK and institutional and ACURO approval obtained we are well positioned to begin the scientific portion of the work.

4. Impact

There has been no significant impact resulting from this work as of now since the scientific portion has only just started.

5. Changes/Problems

The only major change has been the change in institution for the contract. This process took some time and was longer than anticipated.

6. Products

Nothing to Report.

7. Participants & Other Collaborating Organizations

Due to the change in institutions and lengthy amount of time to transfer the contract (just recently transferred August 2016) limited amount of time was spent on this project.

Warren J. Alilain, Ph.D.

Principal Investigator

Nearest person month worked: 1

Dr. Alilain is the Principal Investigator of this project and therefore keeps updated and knowledgeable of the applicable fields (SCI, respiratory plasticity, experimental interventions, etc.). He is also the primary author of the Animal Protocols submitted to ACURO and the University of Kentucky IACUC.

Frank J. Jacono, M.D.

Optional Qualified Collaborator

Nearest person month worked: 1

Dr. Jacono is the Optional Qualified Collaborator of this project and helps oversee the quantification, analysis, and interpretation of the various quantitative measures, as well as the ventilatory pattern variability evaluations.

There is nothing to report in levels of active other support as described in the transfer application documents.

8. Special Reporting Requirements

please see attached Quad Chart in Appendix

9. Appendices – please see quad chart

Improving Survival and Promoting Respiratory Motor Function After Cervical Spinal Cord Injury

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PI: Warren J. Alilain, Ph.D.



Study/Product Aim(s)

The major goals of the project are to:

- 1) Obtain regulatory review and approval by USAMRMC Animal Care and Use Review Office (ACURO) and local Institutional Animal Care and Use Committee (IACUC).
- 2) Test the hypothesis that inhibiting PTEN through bpV will promote recovery of respiratory motor function after cervical SC contusion.
- 3) Test the hypothesis that increasing respiratory drive immediately after cervical contusion will promote survival and independence immediately after cervical SCI.
- 4) Test the hypothesis that respiratory motor patterns and variability are surrogate endpoints that accurately predict functional improvement after cervical SC contusion and intervention.



Our work seeks to improve survival and restore breathing function after cervical spinal cord injury. Left image is of Matt Hampson, an individual with a cervical SCI, on a ventilator which helps enable him to breathe. We want to remove the need for mechanical ventilation. Photo from: www.spinal-research.org.
<http://www.spinal-research.org/news/spinal-research-supporter-matt-hampson-speaks-about-spinal-cord-injury-on-channel-4%E2%80%99s-embarrassing-bodies/>

Schedule

Activities	CY	15	16	17	18	19
IACUC and ACURO Approval		■				
Test bpV for recovery			■	■	■	
Test drug to improve survival					■	■
Evaluate variability			■	■	■	■

Created: 12/23/2015; Modified: 8/10/16

Goals/Milestones

Milestone: Local IRB/IACUC Approval – obtained ☒

Milestone: HRPO/ACURO Approval – obtained ☒

Milestone 1: Respiratory motor outcomes following treatments will be quantified.

Milestone 2: Optimal bpV dosage for improved respiratory motor determined mediated by damaged pathways will be determined.

Milestone 3: The effects of bpV treatment on tissue sparing, sprouting of 5-HT fibers, and regeneration associated signaling molecules will be quantified.

Milestone 4: Respiratory motor outcomes following bpV and rehabilitation will be quantified.

Milestone 5: The effects of bpV treatment and IH rehabilitation on SC tissue will be quantified.

Milestone 1: The effect of increasing respiratory drive with theophylline administration on improving survival and independence on mechanical ventilation immediately after cervical SCI will be quantified.

Milestone 2: Lesion volume will be characterized and quantified.

Milestone 1: Correlate patterns of altered ventilatory pattern variability with the severity of SCI, survival and response to pharmacological intervention (bpV and theophylline).